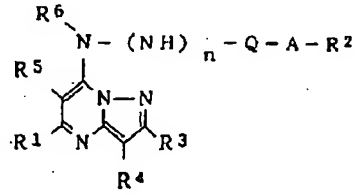
(57) Abstract

Object

To put forward an adenosine potentiator effective in prevention and treatment of myocardial infarction and cerebral infarction.

Method of Solution

Adenosine potentiator, wherein for example, effective ingredient comprises pyrazolo[1,5-a] pyrimidine derivatives represented by general formula

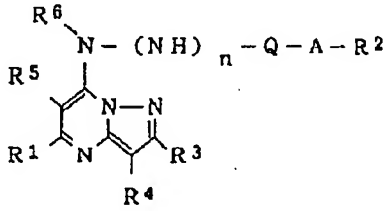


such as 5-n-butyl-7-(3,4,5-trimethoxy benzoylamino) pyrazolo[1,5-a]pyrimidine and the like.

Patent Claims

Claim 1

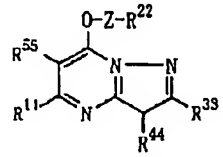
An adenosine potentiator containing an effective dose of an effective component comprising at least one species selected from pyrazolo[1,5-a]pyrimidine derivatives represented by general formula (1)



[wherein, R^1 denotes a hydrogen atom, lower alkyl group optionally having a thienyl group, lower alkoxy group, lower alkylthio group, oxo group, carboxyl group or hydroxyl group as a substituent, cycloalkyl group, thienyl group, furyl group, lower alkenyl group or a phenyl group optionally having 1-3 substituent groups selected fromower alkyl group, lower alkoxy

group, phenylthio group and halogen atom, R^2 denotes a naphthyl group, cycloalkyl group, furyl group, thienyl group, pyridyl group optionally substituted by halogen atom, phenoxy group optionally substituted by halogen atom, or phenyl group optionally having 1-3 substituent groups selected from lower alkyl group, lower alkoxy group, halogen atom, nitro group, halogen substituted-lower alkyl group, halogen substituted-lower alkoxy group, lower alkoxy carbonyl group, hydroxyl group, phenyl lower alkoxy group, amino group, cyano group, lower alkanoyloxy group, phenyl group and di lower alkoxy phosphoryl lower alkyl group, R^3 denotes a hydrogen atom, phenyl group or lower alkyl group, R^4 denotes a hydrogen atom, halogen atom, lower alkyl group, lower alkoxy carbonyl group, phenyl lower alkyl group or a phenyl group optionally having a phenylthio group as a substituent, R^5 denotes a hydrogen atom or a lower alkyl group, R^6 denotes a hydrogen atom, lower alkyl group, phenyl lower alkyl group or a benzoyl group having 1-3 substituent groups selected from lower alkoxy group, halogen substituted-lower alkyl group and halogen atom, and wherein moreover, R^1 and R^5 may link together to form a lower alkylene group; Q denotes a carbonyl group or sulfonyl group, A denotes a single bond, lower alkylene group or lower alkenylene group, and n denotes 0 or 1]

and pyrazolo[1,5-a]pyrimidine derivatives represented by general formula (2)



[wherein, R^{11} denotes a lower alkyl group, R^{22} denotes a phenyl group which has 1-3 lower alkoxy groups as substituents, R^{33}, R^{44} and R^{55} each denote a hydrogen atom and Z denotes a lower alkylene group],

together with a non-toxic carrier.

Claim 2

An adenosine potentiator in accordance with Claim 1, wherein the effective ingredient is selected from compounds of general formula (2) in accordance with Claim 1 and the compounds of general formula (1) in accordance with Claim 1 wherein R^4, R^5 and R^6 are hydrogen atoms, Q is carbonyl group, A is single bond and n is 0.

Claim 3

An adenosine potentiator in accordance with Claim 2, wherein the effective ingredient is selected from compounds of general formula (1) in accordance with Claim 1 wherein R^2 is phenyl group having 3 lower alkoxy groups as substituents, and the compounds of general formula (2) in accordance with Claim 1 wherein R^{22} is phenyl group having 3 lower alkoxy groups as substituents.

Claim 4

An adenosine potentiator in accordance with Claim 3, wherein the effective ingredient is selected from the compounds of general formula (1) in accordance with Claim 1 wherein R^1 is n-propyl or n-butyl group, and the compounds of general formula (2) in accordance with Claim 1 wherein R^{11} is n-butyl.

Claim 5

An adenosine potentiator in accordance with Claim 4, wherein the effective ingredient is selected from 5-n-butyl-7-(3,4,5-trimethoxy benzoylamino) pyrazolo[1,5-a]pyrimidine, 5-n-propyl-7-(3,4,5-trimethoxy benzoylamino) pyrazolo[1,5-a]pyrimidine, 5-n-butyl-2-methyl-7-(3,4,5-trimethoxy benzoylamino) pyrazolo[1,5-a]pyrimidine and 5-n-butyl-7-(3,4,5-trimethoxy benzoyloxy) pyrazolo[1,5-a]pyrimidine.

Claim 6

An adenosine potentiator in accordance with Claim 5, wherein the effective ingredient is 5-n-butyl-7-(3,4,5-trimethoxy benzoylamino) pyrazolo[1,5-a]pyrimidine.

Claim 7

Prevention and treatment agent of myocardial infarction and/or cerebral infarction characterised by containing effective dose of at least one of the pyrazolo[1,5-a]pyrimidine derivatives represented by general formula (1) and general formula (2) in accordance with Claim 1, together with a non-toxic carrier.

Claim 8

The angina pectoris preventative agent characterised by containing effective dose of at least

one of the pyrazolo[1,5-a]pyrimidine derivatives represented by general formula (1) and general formula (2) in accordance with Claim 1, together with a non-toxic carrier.

Detailed Description of the Invention

(0001)

Technical Sphere of the Invention

This invention relates to a novel adenosine potentiator.

(0002)

Technology of the Prior Art

Myocardial infarction and cerebral infarction and the like are known as diseases which increase with age. Diseases such as these are said to originate when tissue becomes ischemic due to occlusion and constriction of blood vessels, but generally, when tissue, particularly the heart, falls into ischemia state, the autoregulation ability functions so that microvessels expand accompanied by lowering of blood flow pressure, to maintain a constant bloodflow rate. Moreover, it has been elucidated that adenosine has important role as control factor in this autoregulation ability (J. Physiol, 204, 317 (1963)).

(0003)

Namely, in ischemic myocardium, the mechanism is that adenosine is produced from ATP (adenosine triphosphate) which is energy source, and this adenosine expands arterioles.

(0004)

Moreover, adenosine is known to have angiogenesis action and platelet aggregation inhibitory action in addition to the aforesaid arteriole dilation action, and fulfill the role of protection of ischemia myocardium and reperfusion disorder relief.

(0005)

However, the regenerated adenosine is taken in by erythrocyte and myocardial cell, and moreover is degraded by enzyme, and it is rapidly eliminated. However, recently the agent which inhibits this, and maintained adenosine concentration within tissue, which are called the adenosine potentiators were developed. As representative thereof, there are for example

dipyridamole and dilazep, and ones such as these are used as supporting drugs of nitrous acid agents, calcium antagonists and so on, and use as prophylactic of angina attack is examined.

(0006)

Problems to be Overcome by this Invention

The object of this invention is to put forward the following, namely, new substance with adenosine potentiation action with scarcely any of the side effects which are seen in those compounds and which are structurally unrelated to those compounds, and the adenosine potentiator using this substance.

(0007)

Study group of these inventors have been performed research and analysis of the synthesis of various kinds of compound and their pharmacologic actions, with the object of development of drug preparation effective ingredient compound, and in that process, succeeded precedently in synthesis of series of pyrazolopyrimidine derivative having strong analgesia action, and invention concerned with compound such as these or the like was applied (WO95 /35298 and WO97 /11946).

(0008)

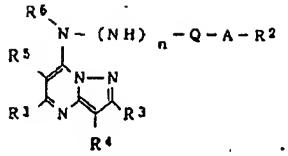
In subsequent investigations, these inventors, have made a new discovery, that the aforesaid series of compounds have adenosine potentiation action, separate from their analgesic action and moreover unrelated to that action, and in addition, markedly reduced side effects. This invention was completed based on this discovery here.

(0009)

Means to Overcome these Problems

In other words, adenosine potentiator is put forward, wherein the effective ingredient comprises at least one member selected from the pyrazolo[1,5-a]pyrimidine derivatives which represented by following general formula (1) and general formula (2) in accordance with this invention.

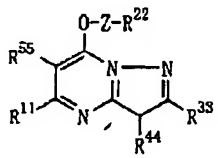
(0010)



(0011)

In the aforesaid general formula (1), R^1 denotes a hydrogen atom, lower alkyl group optionally having a thienyl group, lower alkoxy group, lower alkylthio group, oxo group, carboxyl group or hydroxyl group as a substituent, cycloalkyl group, thienyl group, furyl group, lower alkenyl group or la phenyl group optionally having 1-3 substituent groups selected fromower alkyl group, lower alkoxy group, phenylthio group and halogen atom, R^2 denotes a naphthyl group, cycloalkyl group, furyl group, thienyl group, pyridyl group optionally substituted by halogen atom, phenoxy group optionally substituted by halogen atom, or phenyl group optionally having 1-3 substituent groups selected from lower alkyl group, lower alkoxy group, halogen atom, nitro group, halogen substituted-lower alkyl group, halogen substituted-lower alkoxy group, lower alkoxy carbonyl group, hydroxyl group, phenyl lower alkoxy group, amino group, cyano group, lower alkanoyloxy group, phenyl group and di lower alkoxy phosphoryl lower alkyl group, R^3 denotes a hydrogen atom, phenyl group or lower alkyl group, R^4 denotes a hydrogen atom, halogen atom, lower alkyl group, lower alkoxy carbonyl group, phenyl lower alkyl group or a phenyl group optionally having a phenylthio group as a substituent, R^5 denotes a hydrogen atom or a lower alkyl group, R^6 denotes a hydrogen atom, lower alkyl group, phenyl lower alkyl group or a benzoyl group having 1-3 substituent groups selected from lower alkoxy group, halogen substituted-lower alkyl group and halogen atom, and wherein moreover, R^1 and R^5 may link together to form a lower alkylene group; Q denotes a carbonyl group or sulfonyl group, A denotes a single bond, lower alkylene group or lower alkenylene group, and n denotes 0 or 1.

(0012)



(0013)

In aforesaid general formula (2), R^{11} denotes a lower alkyl group, R^{22} denotes a phenyl group which has 1-3 lower alkoxy groups as substituents, R^{33}, R^{44} and R^{55} each denote a hydrogen atom and Z denotes a lower alkylene group.

(0014)

Each derivative represented by the aforesaid general formula (1) and general formula (2) demonstrates excellent adenosine potentiation action in each case, and moreover, it has the characteristic that it is almost free from side effects such as nausea, headache, vertigo, being feverish or the like which is common in a substance having the kind of adenosine potentiation action of the prior art.

(0015)

Conditions for Carrying out this Invention

As each group in general formula (1) denoting effective ingredient of adenosine potentiator of this invention, for example, each of the following groups can be given as examples. Namely, as lower alkyl group, straight chain or branched chain state lower alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl group and the like can be given as examples.

(0016)

As cycloalkyl group, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl group and the like can be given as examples.

(0017)

As lower alkoxy group, methoxy, ethoxy, propoxy, isopropoxy, butoxy, pentyloxy, hexyloxy groups and the like can be given as examples.

(0018)

As lower alkyl thio group, methylthio, ethylthio, propylthio, butylthio, pentyl thio, hexyl thio group and the like can be given as examples.

(0019)

Fluorine, chlorine, bromine and iodine atom are included in halogen atom.

(0020)

As halogen substituted lower alkyl group, trifluoromethyl, pentafluoro ethyl, heptafluoro propyl, nonafluoro butyl, undeca fluoro pentyl, trideca fluoro hexyl group and the like can be given as examples.

(0021)

As halogen substituted lower alkoxy group, trifluoromethoxy, pentafluoro ethoxy, heptafluoropropoxy, nonafluoro butoxy, undeca fluoro pentyloxy, trideca fluoro hexyloxy group can be given as examples.

(0022)

As lower alkoxycarbonyl group, methoxycarbonyl, ethoxycarbonyl, propoxy carbonyl, isopropoxy carbonyl, butoxycarbonyl, pentyloxy carbonyl, hexyloxy carbonyl group can be given as examples.

(0023)

As dilower alkoxy phosphoryl lower alkyl group, dimethoxyphosphoryl methyl, diethoxy phosphoryl methyl, dipropoxy phosphoryl methyl, diisopropoxy phosphoryl methyl, dibutoxy phosphoryl methyl, dipentyloxy phosphoryl methyl, dihexyl oxy phosphoryl methyl, 2-(dimethoxyphosphoryl) ethyl, 2-(diethoxy phosphoryl) ethyl, 3-(diethoxy phosphoryl) propyl group and the like can be given as examples.

(0024)

As naphthyl group, 1-naphthyl, 2-naphthyl group are included.

(0025)

As lower alkylene group, methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene group and the like can be given as examples.

(0026)

As lower alkenylene group, vinylene, propenylene group and the like can be given as examples.

(0027)

As pyridyl group optionally substituted by halogen atom, 2-pyridyl, 3-pyridyl, 4-pyridyl, 6-chloro-2-pyridyl, 5-chloro-2-pyridyl, 4-chloro-2-pyridyl, 3-chloro-2-pyridyl, 6-chloro-3-pyridyl, 5-chloro-3-pyridyl, 4-chloro-3-pyridyl, 2-chloro-3-pyridyl, 2-chloro-4-pyridyl, 3-chloro-4-pyridyl, 6-fluoro-3-pyridyl, 6-bromo-3-pyridyl, 6-iodo-3-pyridyl group and the like can be given as examples.

(0028)

As phenoxy group optionally substituted by halogen atom, phenoxy, 2-chlorophenoxy, 3-chlorophenoxy, 4-chlorophenoxy, 4-fluoro phenoxy, 4-bromo phenoxy, 4-iodo phenoxy group and the like can be given as examples.

(0029)

In thienyl group, 2-thienyl and 3-thienyl group are included, and also 2-furyl and 3-furyl group are included in furyl group.

(0030)

As lower alkenyl group, vinyl, allyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl group and the like can be given as examples.

(0031)

As phenyl lower alkyl group, benzyl, 1-phenylethyl, 2-phenylethyl, 3-phenylpropyl, 4-phenylbutyl, 5-phenyl pentyl, 6-phenylhexyl group and the like can be given as examples.

(0032)

As phenyl lower alkoxy group, benzyloxy, 2-phenyl ethoxy, 3-phenyl propoxy, 4-phenyl butoxy, 5-phenyl pentyloxy, 6-phenylhexyl oxy group and the like can be given as examples.

(0033)

As lower alkanoyloxy group, acetoxy, propionyloxy, butyryl oxy, valeryl oxy, pivaloyloxy, hexanoyloxy, heptanoyloxy group and the like can be given as examples.

(0034)

As lower alkyl group optionally having thienyl group, lower alkoxy group, lower alkyl thio group, oxo group, carboxyl group or hydroxyl group as substituent, in addition to the aforesaid unsubstituted lower alkyl group, 2-thienylmethyl, 3-thienylmethyl, 1-(2-thienyl) ethyl, 1-(3-thienyl) ethyl, 2-(2-thienyl) ethyl, 2-(3-thienyl) ethyl, 3-(2-thienyl) propyl, 4-(2-thienyl) butyl, 5-(2-thienyl) pentyl, 6-(2-thienyl) hexyl, methoxymethyl, ethoxymethyl, propoxymethyl, butoxymethyl, pentyloxy methyl, hexyloxy methyl, 1-methoxyethyl, 2-methoxyethyl, 3-methoxy propyl, 4-methoxybutyl, 5-methoxy pentyl, 6-methoxy hexyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 1-hydroxypropyl, 2-hydroxypropyl, 3-hydroxypropyl, 3-hydroxybutyl, 4-hydroxy pentyl, 5-hydroxyhexyl, methylthiomethyl, ethylthio methyl, propylthio methyl, butylthio methyl, pentyl thiomethyl, hexyl thiomethyl, 2-methylthio ethyl, 3-methylthio propyl, 4-methylthio butyl, 5-methylthio pentyl, 6-methylthio hexyl, formyl, formylmethyl, acetyl, 2-formyl ethyl, 2-oxopropyl, propionyl, 3-formyl propyl, 3-oxobutyl, 2-oxobutyl, butyryl, 4-formyl butyl, 4-oxo pentyl, 3-oxo pentyl, 2-oxo pentyl, valeryl, 5-formyl pentyl, 5-oxohexyl, 4-oxohexyl, 3-oxohexyl, 2-oxohexyl, hexanoyl, carboxymethyl, 2-carboxyethyl, 3-carboxypropyl, 4-carboxybutyl, 5-carboxy pentyl, 6-carboxy hexyl group and the like can be given as examples.

(0035)

As phenyl group optionally containing 1-3 groups selected from the lower alkyl group, lower alkoxy group, phenylthio group and halogen atom as substituent, phenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 4-ethylphenyl, 4-propyl phenyl, 4-butylphenyl, 4-t-butylphenyl, 4-pentylphenyl, 4-hexyl phenyl, 2,3-dimethyl phenyl, 2,4-dimethyl phenyl, 2,5-dimethyl phenyl, 2,6-dimethyl phenyl, 3,4-dimethyl phenyl, 3,5-dimethyl phenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 4-ethoxyphenyl, 4-propoxy phenyl, 4-butoxy phenyl, 4-pentyloxyphenyl, 4-hexyloxyphenyl, 2,3-dimethoxyphenyl, 2,4-dimethoxyphenyl, 2,5-dimethoxyphenyl, 2,6-dimethoxyphenyl, 3,4-dimethoxyphenyl, 3,5-

dimethoxyphenyl, 3,4,5-trimethoxyphenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 4-bromo phenyl, 4-iodophenyl, 4-fluorophenyl, 4-(phenylthio) phenyl, 3-(phenylthio) phenyl, 2-(phenylthio) phenyl group and the like can be given as examples.

(0036)

As phenyl group optionally containing 1-3 groups selected from the lower alkyl group, lower alkoxy group, halogen atom, nitro group, halogen substituted lower alkyl group, halogen substituted lower alkoxy group, lower alkoxycarbonyl group, hydroxyl group, phenyl lower alkoxy group, amino group, cyano group, lower alkanoyloxy group, phenyl group and dilower alkoxy phosphoryl lower alkyl group as substituent, each of the following group can be given as examples.

(0037)

Namely phenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 4-ethylphenyl, 4-propyl phenyl, 4-butylphenyl, 4-t-butylphenyl, 4-pentylphenyl, 4-hexyl phenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 4-ethoxyphenyl, 4-propoxy phenyl, 4-butoxy phenyl, 4-pentyloxyphenyl, 4-hexyloxyphenyl, 2,3-dimethoxyphenyl, 2,4-dimethoxyphenyl, 2,5-dimethoxyphenyl, 2,6-dimethoxyphenyl, 3,4-dimethoxyphenyl, 3,5-dimethoxyphenyl, 2,3,4-trimethoxyphenyl, 2,3,5-trimethoxyphenyl, 2,3,6-trimethoxyphenyl, 2,4,5-trimethoxyphenyl, 2,4,6-trimethoxyphenyl, 3,4,5-trimethoxyphenyl, 3,4,5-tri ethoxyphenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-bromo phenyl, 3-bromo phenyl, 4-bromo phenyl, 4-iodophenyl, 2,3-dichlorophenyl, 2,4-dichlorophenyl, 2-nitrophenyl, 3-nitrophenyl, 4-nitrophenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 4-pentafluoro ethylphenyl, 4-heptafluoro propyl phenyl, 4-nonafluoro butylphenyl, 4-undeca fluoro pentylphenyl, 4-trideca fluoro hexyl phenyl, 2-carbomethoxyphenyl, 3-carbomethoxyphenyl, 4-carbomethoxyphenyl, 4-ethoxycarbonyl phenyl, 4-propoxy carbonyl phenyl, 4-butoxycarbonyl phenyl, 4-pentyloxy carbonyl phenyl, 4-hexyloxy carbonyl phenyl, 2-biphenyl, 3-biphenyl, 4-biphenyl, 2-(diethoxy phosphoryl methyl) phenyl, 3-(diethoxy phosphoryl methyl) phenyl, 4-(diethoxy phosphoryl methyl) phenyl, 4-(dimethoxyphosphoryl methyl) phenyl, 4-(diisopropoxy phosphoryl methyl) phenyl, 3,5-dimethoxy-4-ethoxyphenyl, 3,5-dimethoxy-4-propoxy phenyl, 4-butoxy-3,5-dimethoxyphenyl, 3,5-dimethoxy-4-pentyloxyphenyl, 3,5-dimethoxy-4-

hexyloxyphenyl, 2,3-bis (trifluoromethyl) phenyl, 2,4-bis (trifluoromethyl) phenyl, 2,5-bis (trifluoromethyl) phenyl, 2,6-bis (trifluoromethyl) phenyl, 3,4-bis (trifluoromethyl) phenyl, 3,5-bis (trifluoromethyl) phenyl, 3,5-dimethoxy-4-hydroxyphenyl, 3,5-diethoxy-4-hydroxyphenyl, 3,5-dipropoxy-4-hydroxyphenyl, 4-benzyloxy-3,5-dimethoxyphenyl, 4-benzyloxy-3,5-diethoxy phenyl, 3,5-dimethoxy-4-(2-phenyl ethoxy) phenyl, 4-acetoxy-3,5-dimethoxyphenyl, 3,5-dimethoxy-4-propionyloxy phenyl, 2-chloro-3,5-dimethoxyphenyl, 4-chloro-3,5-dimethoxyphenyl, 4-bromo-3,5-dimethoxyphenyl, 3,5-dimethoxy-4-iodophenyl, 3,5-dichloro-4-methoxyphenyl, 3,5-dichloro-4-ethoxyphenyl, 2-aminophenyl, 3-aminophenyl, 4-aminophenyl, 2-cyanophenyl, 3-cyanophenyl, 4-cyanophenyl, 4-trifluoromethoxyphenyl, 3-trifluoromethoxyphenyl, 2-trifluoromethoxyphenyl, 4-pentafluoro ethoxyphenyl, 4-heptafluoropropoxy phenyl, 4-nonafluoro butoxy phenyl, 4-undeca fluoro pentyloxyphenyl, 4-trideca fluoro hexyloxyphenyl, 3,5-bis (trifluoromethoxy) phenyl, 3,4,5-tris (trifluoromethoxy) phenyl group and the like can be given as examples.

(0038))

As phenyl group optionally having phenylthio group as substituent, phenyl, 4-(phenylthio) phenyl, 3-(phenylthio) phenyl, 2-(phenylthio) phenyl group and the like can be given as examples.

(0039)

As benzoyl group containing 1-3 groups selected from the lower alkoxy group, halogen substituted lower alkyl group and halogen atom as substituent, 2-chlorobenzoyl, 3-chlorobenzoyl, 4-chlorobenzoyl, 2-fluorobenzoyl, 2-bromobenzoyl, 2-iodobenzoyl, 2,4-dichlorobenzoyl, 3,4-dichlorobenzoyl, 2,5-dichlorobenzoyl, 2,6-dichlorobenzoyl, 2-trifluoromethyl benzoyl, 3-trifluoromethyl benzoyl, 4-trifluoromethyl benzoyl, 3, 5-bis (trifluoromethyl) benzoyl, 3, 4, 5-tris (trifluoromethyl) benzoyl, 2-methoxybenzoyl, 3-methoxybenzoyl, 4-methoxybenzoyl, 2,3-dimethoxybenzoyl, 2,4-dimethoxybenzoyl, 3,5-dimethoxybenzoyl, 3, 4, 5-trimethoxy benzoyl, 2-ethoxy benzoyl, 2-propoxy benzoyl, 2-butoxy benzoyl, 2-pentyloxy benzoyl, 2-hexyloxy benzoyl group and the like can be given as examples.

(0040)

As each group in general formula (2) denoting effective ingredient of adenosine potentiator of this invention, for example each of the following groups can be given as examples. Namely, as lower alkyl group, straight chain or branched chain state lower alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl group and the like can be given as examples.

(0041)

As lower alkylene group, methylene, ethylene, ethylidene, trimethylene, tetramethylene, pentamethylene, hexamethylene and the like and the like can be given as examples.

(0042)

As phenyl group containing 1-3 lower alkoxy groups as substituent, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 4-ethoxyphenyl, 4-propoxy phenyl, 4-butoxy phenyl, 4-pentyloxyphenyl, 4-hexyloxyphenyl, 2,4-dimethoxyphenyl, 3,4-dimethoxyphenyl, 3,5-dimethoxyphenyl, 2, 4, 5-trimethoxyphenyl, 3, 4, 5-trimethoxyphenyl, 2, 4, 6-trimethoxyphenyl, 4-ethoxy-3,5-dimethoxyphenyl group and the like can be given as examples.

(0043)

Pyrazolo[1,5-a]pyrimidine derivatives which represented by general formula (1) and (2) are useful as adenosine potentiators in the prevention and treatment of for example myocardial infarction and cerebral infarction. Moreover, there is not side effect common in prior art adenosine potentiator, and there is not the fear that the said derivative brings hallucination or confusion, or produces addiction and habituation.

(0044)

Compounds of general formula (2), and compounds of general formula (1) wherein R^4, R^5 and R^6 are hydrogen atoms, Q is carbonyl group, A is single bond, and n is 0 can be given as examples of the preferred pyrazolo[1,5-a]pyrimidine derivatives as the aforesaid adenosine potentiator effective ingredient.

(0045)

Among these pyrazolo[1,5-a]pyrimidine derivatives, particularly (a) compounds of general formula (1) wherein R^2 is phenyl having 3 lower alkoxy groups as substituent and compound of general formula (2) wherein R^{22} is phenyl having 3 lower alkoxy groups as substituent are more preferred, and among these, the compounds of general formula (1) wherein R^1 is n-propyl or n-butyl group and compounds of general formula (2) wherein R^{11} is n-butyl are particularly preferred.

(0046)

As embodiment of most preferred pyrazolo[1,5-a]pyrimidine derivatives, 5-n-butyl-7-(3,4,5-trimethoxy benzoylamino) pyrazolo[1,5-a]pyrimidine, 5-n-propyl-7-(3,4,5-trimethoxy benzoylamino) pyrazolo[1,5-a]pyrimidine, 5-n-butyl-2-methyl-7-(3,4,5-trimethoxy benzoylamino) pyrazolo[1,5-a]pyrimidine and 5-n-butyl-7-(3,4,5-trimethoxy benzoyloxy) pyrazolo[1,5-a]pyrimidine can be given as examples, and among these, 5-n-butyl-7-(3,4,5-trimethoxy benzoylamino) pyrazolo[1,5-a]pyrimidine is ideal.

(0047)

Effective ingredient compound represented by general formula (1) of this invention can be produced using various processes, and, as embodiment thereof, for example, process in accordance with the aforesaid WO95 /35298 bulletin can be given as example.

(0048)

Typically, 7-hydroxy pyrazolo[1,5-a]pyrimidine species are obtained by condensation reaction of 3-aminopyrazole species and suitable carboxylate ester, then this is halogenated to make 7-halopyrazolo[1,5-a]pyrimidine species, and this is further treated with ammonia water or hydrazine, to converted into 7-amino compound, and by reacting this with a halogen compound, it is possible to obtain effective ingredient compound of this invention.

(0049)

Moreover effective ingredient compound represented by general formula (2) of this invention can be produced using various process, too. As embodiment thereof, for example, process in accordance with the aforesaid WO97 /11946 bulletin can be given as example.

(0050)

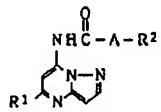
Typically, in the same way as in compound of the said general formula (1), 7-halo pyrazolo [1,5-a]pyrimidine species are obtained, and by reacting this with a suitable alcohol compound, it is possible to obtain effective ingredient compound of this invention.

(0051)

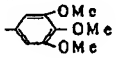
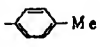
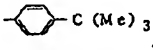
As embodiment of the obtained effective ingredient compound of the adenosine potentiator of this invention, each compound of Example 1-136 shown in following Table 1-Table 6 is given as example.

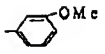
(0052)

Table 1



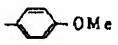
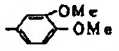
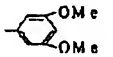
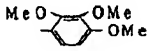
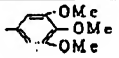
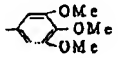
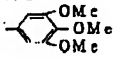
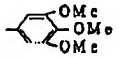
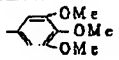
Me: methyl group, Et: ethyl group, nPr: n-propyl group,
nBu: n-butyl group, nPe: n-pentyl group, Ph: Phenyl group

Example No.	R1	R2	A	Melting point (°C) (Re-crystallisation solvent)
1	nBu		Single bond	127-129 (diethylether – n-hexane)
2	nBu	Ph	Single bond	83-85 (ethyl acetate – n-hexane)
3	nBu		Single bond	102-104 (n-hexane)
4	nBu		Single bond	94-95 (n-hexane)
5	nBu		Single bond	83-84 (n-hexane)
6	nBu		Single bond	^{1}H-NMR (CDCl$_3$) 0.97(3H,t,J=7.3), 1.37(9H,s), 1.4-1.5(2H,m), 1.7-1.9(2H,m), 2.86(2H,t,J=7.8), 6.57(1H,d,J=2.3), 7.58(1H,d,J=8.7), 7.77(1H,s), 7.97(1H,d,J=8.7), 8.03(1H,d,J=2.3), 10.0(1H,brs)
7	nBu		Single bond	82-84 (n-hexane)

8	nBu		Single bond	49-51 (n-hexane)

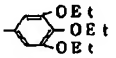
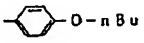
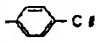
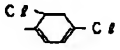
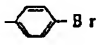
(0053)

Table 1 (continued)

Example No.	R1	R2	A	Melting point (°C) (Re-crystallisation solvent)
9	nBu		Single bond	108-109 (n-hexane)
10	nBu		Single bond	129-132 (n-hexane)
11	nBu		Single bond	143-144 (diethylether – n-hexane)
12	nBu		Single bond	101-103 (diethylether – n-hexane)
13	nBu		Single bond	92-94 (diethylether – n-hexane)
14	nBu		Single bond	115-117 (ethyl acetate – n-hexane)
15	Et		Single bond	141-143 (ethyl acetate – n-hexane)
16	nPr		Single bond	119-121 (diethylether – n-hexane)
17			Single bond	198-201 (ethyl acetate – n-hexane)
18	nPe		Single bond	116-118 (n-hexane)
19	Ph		Single bond	185-187 (ethyl acetate – n-hexane)

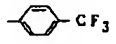
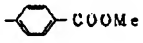
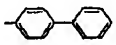
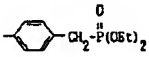
(0054)

Table 1 (continued)

Example No.	R1	R2	A	Melting point (°C) (Re-crystallisation solvent)
20	nBu		Single bond	100-102 (diethylether – n-hexane)
21	nBu		Single bond	87-90 (n-hexane)
22	nBu		Single bond	99-100 (n-hexane)
23	nBu		Single bond	107-109 (diethylether)
24	nBu		Single bond	81-82 (n-hexane)
25	nBu		Single bond	92-94 (diethylether)
26	nBu		Single bond	97-99 (n-hexane)
27	nBu		Single bond	93-95 (n-hexane)
28	nBu		Single bond	97-99 (n-hexane)
29	nBu		Single bond	133-135 (ethyl acetate – n-hexane)
30	nBu		Single bond	143-145 (ethyl acetate – n-hexane)

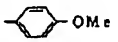
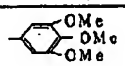
(0055)

Table 1 (continued)

Example No.	R1	R2	A	Melting point (°C) (Re-crystallisation solvent)
31	Et		Single bond	125-127 (diethylether – n-hexane)
32	nBu		Single bond	84-87 (n-hexane)
33	nBu		Single bond	95-97 (n-hexane)
34	nBu		Single bond	122-123 (n-hexane)
35	nBu		Single bond	139-141 (ethyl acetate – n-hexane)
36	nBu		Single bond	119-121 (ethyl acetate – n-hexane)
37	nBu		Single bond	57-60 (ethyl acetate – n-hexane)
38	nBu		Single bond	82-84 (diethylether – n-hexane)
39	nBu		Single bond	103-105 (ethyl acetate – n-hexane)
40	nBu		Single bond	92-93 (diethylether – n-hexane)
41	nBu	Ph	$-CH_2-$	80-82 (diethylether – n-hexane)

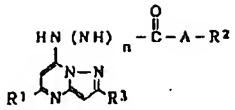
(0056)

Table 1 (continued)

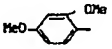
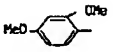
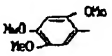
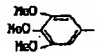
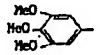
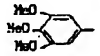
Example No.	R1	R2	A	Melting point (°C) (Re-crystallisation solvent)
42	nBu		$-CH_2-$	73-75 (diethylether – n-hexane)
43	nBu	Ph	$-C_2H_4-$	^1H-NMR (CDCl$_3$) 0.95(3H,t,J=7.3), 1.3-1.5 (2H,m), 1.7-1.8(2H,m), 2.60 (2H,t,J=7.8), 2.88(2H,t,J=7.6), 3.09(2H,t,J=7.5), 6.53 (1H,d,J=2.2), 7.2-7.3(5H,m), 7.60(1H,s), 7.95(1H,d,J=2.2), 9.23(1H,brs)
44	nBu	PhO-	$-CH_2-$	108-109 (n-hexane)
45	nBu		$-CH_2-$	140-142 (ethyl acetate – n-hexane)
46	nBu		-CH=CH-	134-137 (ethyl acetate – n-hexane)

(0057)

Table 2



Me: methyl group, Et: ethyl group, nPr: n-propyl group,
nBu: n-butyl group, tBu: t-butyl group, nPe: n-pentyl group,
Ph: Phenyl group, Ac: Acetyl group.

Example No.	R1	R2	R3	A	n	Melting point (°C) (Re-crystallisation solvent)
47	nBu		H	Single bond	0	^{1}H-NMR (CDCl$_3$) 0.95(3H,t,J=7.4), 1.2-2.1 (14H,m), 2.4-2.6(3H,m),2.81 (2H,t,J=7.6), 8.54(1H,d,J=2.2),7.62(1H,s), 8.00(1H,d, J=2.2),9.29(1H,brs)
48	nBu		H	Single bond	0	141-142 (ethanol – n-hexane)
49			H	Single bond	0	209-211 (methylene chloride – ethyl acetate)
50			H	Single bond	0	206-208 (methylene chloride – ethyl acetate)
51	nBu		H	Single bond	0	136-137 (ethanol – n-hexane)
52	Me		H	Single bond	0	173-175 (ethanol – n-hexane)
53	nBu		Me	Single bond	0	127-129 (ethanol – n-hexane)
54	CH_2=CH-C_2H_4-		H	Single bond	0	104-106 (ethyl acetate – n-hexane)

(0058)

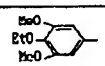
Table 2 (continued)

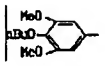
Example No.	R1	R2	R3	A	n	Melting point (°C) (Re-crystallisation solvent)
55	Et-O-CH_2-		H	Single bond	0	138-140 (ethyl acetate – n-hexane)
56			H	Single bond	0	163-165 (chloroform – ethyl acetate)
57			H	Single bond	0	166-168 (ethyl acetate – n-hexane)
58			H	Single bond	0	193-195 (methylene chloride - diethylether)
59			H	Single bond	0	174-176 (methylene chloride - diethylether)
60			H	Single bond	0	203-205 (methylene chloride - diethylether)
61			H	Single bond	0	175-177 (methylene chloride - ethyl acetate)
62			H	Single bond	0	192-194 (methylene chloride - diethylether)
63			H	Single bond	0	181-193 (methylene chloride - diethylether)
64			H	Single bond	0	224-226 (methylene chloride - diethylether)

65			H	Single bond	0	214-216 (methylene chloride - diethylether)

(0059)

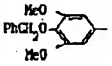
Table 2 (continued)

Example No.	R1	R2	R3	A	n	Melting point (°C) (Re-crystallisation solvent)
66			H	Single bond	0	190-192 (methylene chloride - diethylether)
67			H	Single bond	0	222-224 (chloroform – ethyl acetate)
68			H	Single bond	0	193-195 (chloroform – ethyl acetate)
69			H	Single bond	0	189-191 (methylene chloride - diethylether)
70			H	Single bond	0	174-176 (methylene chloride - diethylether)
71			H	Single bond	0	191-193 (methylene chloride - diethylether)
72			H	Single bond	0	198-200 (methylene chloride - ethyl acetate)
73			H	Single bond	0	157-159 (ethyl acetate)
74	nBu		H	Single bond	0	159-161 (ethanol – n-hexane)
75	nBu		H	Single bond	0	79-81 (diethylether – n-hexane)

76	nBu		H	Single bond	0	98-100 (n-hexane)

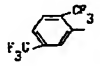
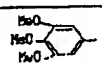
(0060)

Table 2 (continued)

Example No.	R1	R2	R3	A	n	Melting point (°C) (Re-crystallisation solvent)
77	nBu		H	Single bond	0	82-85 (ethanol – n-hexane)
78	nBu		H	Single bond	0	158-160 (ethyl acetate – n-hexane)
79	nBu		H	Single bond	0	182-184 (ethyl acetate – n-hexane)
80	nBu		H	Single bond	0	132-135 (ethyl acetate – n-hexane)
81	nBu		H	Single bond	0	111-113 (diethylether – n-hexane)
82	Me		H	Single bond	0	154-155 (ethanol – n-hexane)
83	nPr		H	Single bond	0	139-141 (diethylether – n-hexane)
84			H	Single bond	0	102-104 (n-hexane)
85	nPe		H	Single bond	0	93-95 (n-hexane)
86	Ph		H	Single bond	0	143-145 (diethylether – n-hexane)
87	nBu		H	Single bond	0	46-48 (ethyl acetate – n-hexane)

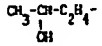
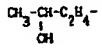
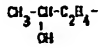
(0061)

Table 2 (continued)

Example No.	R1	R2	R3	A	n	Melting point (°C) (Re-crystallisation solvent)
88	nBu		H	Single bond	0	108-110 (n-hexane)
89	nBu		H	Single bond	0	92.5-94.5 (n-hexane)
90	nBu		H	Single bond	0	106-108 (n-hexane)
91	nBu		H	Single bond	0	123-125 (ethanol – n-hexane)
92	nBu		H	Single bond	0	123-125 (diethylether – n-hexane)
93	nBu		H	Single bond	0	139-140 (ethanol – n-hexane)
94	nBu		H	CH_2	0	121-123 (ethyl acetate – n-hexane)
95	nBu		H	-CH=CH-	0	194-196 (ethanol – n-hexane)
96	nBu		H	Single bond	1	222 (decomposition) (ethanol – n-hexane)
97	Ph		H	Single bond	1	250 (decomposition) (methanol – n-hexane)
98	nBu		H	Single bond	1	247 (decomposition) (ethanol – n-hexane)

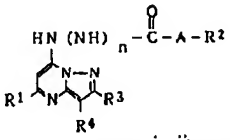
(0062)

Table 2 (continued)

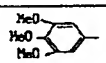
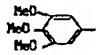
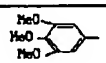
Example No.	R1	R2	R3	A	n	Melting point (°C) (Re-crystallisation solvent)
99	Ph		H	Single bond	1	263 (decomposition) (ethanol – n-hexane)
100			H	Single bond	0	128-130 (methylene chloride – n-hexane)
101			H	Single bond	0	153-155 (ethanol – n-hexane)
102			H	Single bond	0	127-129 (ethyl acetate - n-hexane)

(0063)

Table 3

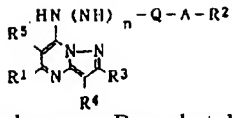


Me: methyl group, nBu: n-butyl group.

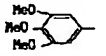
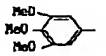
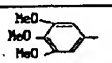
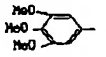
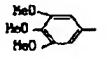
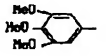
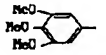
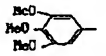
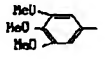
Example No.	R1	R2	R3	R4	A	n	Melting point (°C) (Re-crystallisation solvent)
103	nBu		Me	Cl	Single bond	0	106-108 (ethanol – n-hexane)
104	nBu		H	Cl	Single bond	0	142-143 (ethanol – n-hexane)
105	nBu		H	Br	Single bond	0	146-148 (ethanol – n-hexane)
106	nBu		H	Cl	Single bond	0	133-135 (diethylether – n-hexane)

(0064)

Table 4

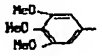
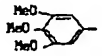
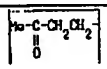
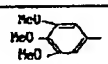
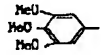
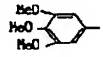
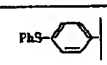
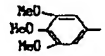
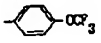


Me: methyl group, Et: ethyl group, nBu: n-butyl group, Ph: phenyl group.

Example No.	R1	R5	R2	R3	R4	Q	A	n	Melting point (° C) (Re-crystallisation solvent)
107	H	H		H	H	C=O	Single bond	0	185-187 (methylene chloride – n-hexane)
108	nBu	H		Me		C=O	Single bond	0	138-140 (ethyl acetate – n-hexane)
109	nBu	H		nBu	H	C=O	Single bond	0	95-97 (ethyl acetate – n-hexane)
110	nBu	H		nBu	Me	C=O	Single bond	0	96-98 (ethyl acetate – n-hexane)
111	nBu	H		Ph	H	C=O	Single bond	0	190-192 (methylene chloride – diethylether)
112	nBu	H		Ph	$PhCH_2$-	C=O	Single bond	0	149-151 (ethyl acetate – n-hexane)
113	nBu	H		Ph		C=O	Single bond	0	111-113 (ethyl acetate – n-hexane)
114	nBu	H		H	nBu	C=O	Single bond	0	81-83 (n-hexane)
115	nBu	H		H	Ph	C=O	Single bond	0	139-141 (ethyl acetate – n-hexane)

(0065)

Table 4 (continued)

Example No.	R1	R5	R2	R3	R4	Q	A	n	Melting point (° C) (Re-crystallisation solvent)
116	nBu	Me		H	H	C=O	Single bond	0	145-147. (methylene chloride - n-hexane)
117	-$CH_2CH_2CH_2CH_2$-			H	H	C=O	Single bond	0	102-104 (methylene chloride - – n-hexane)
118		H		H	H	C=O	Single bond	0	115-117 (methylene chloride - – n-hexane)
119	Et-S-CH_2-	H		H	H	C=O	Single bond	0	80-82 (ethyl acetate – n-hexane)
120	MeS-CH_2CH_2-	H		H	H	C=O	Single bond	0	113-115 (methylene chloride - diethylether)
121		H		H	H	C=O	Single bond	0	179-181 (methylene chloride - diethylether)
122	nBu	H		H	H	C=O	Single bond	0	98-100 (diethylether)
123	nBu	H		H	H	C=O	Single bond	0	73-75 (n-hexane)
124	nBu	H		H	H	C=O	Single bond	0	129-131 (n-hexane)
125	nBu	H		H	H	C=O	Single bond	0	91-93 (diethylether – n-hexane)

126	nBu	H		H	H	C=O	Single bond	0	91-93 (n-hexane)

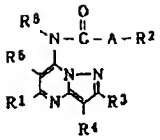
(0066)

Table 4 (continued)

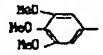
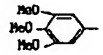
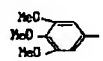
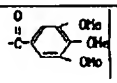
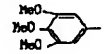
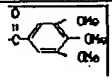
Example No.	R1	R5	R2	R3	R4	Q	A	n	Melting point (° C) (Re-crystallisation solvent)
127	nBu	H	Ph	H	H	SO_2	Single bond	0	over 300°C (ethyl acetate – n-hexane)
128	nBu	H		H	H	SO_2	Single bond	0	over 300°C (ethyl acetate – n-hexane)

(0067)

Table 5



Me: methyl group, nBu: n-butyl group.

Example No.	R1	R5	R2	R3	R4	R6	A	Melting point (°C) (Re-crystallisation solvent)
129	nBu	H		H	H	Me	Single bond	93-95 (ethyl acetate – n-hexane)
130	nBu	H		H	H	Ph-CH_2-	Single bond	^{1}H-NMR(CDCl$_3$) δ 0.76(2H,t,J=7.2), 0.9-1.1(2H,m),1.3-1.4(2H,m), 2.51(2H,t,J=7.4), 3.47(6H,s), 3.74(3H,s), 5.33(2H,brs), 5.83(1H,s), 6.60(2H,s), 6.68(1H,d,J=2.0), 7.1-7.3(5H,m), 8.24(1H,d,J=2.0)
131	nBu	H		H	H		Single bond	127-129 (ethyl acetate – n-hexane)
132	nBu	H		H	H		Single bond	119-121 (diethylether – n-hexane)
133	Me	H		H	H		Single bond	180-182 (methylene chloride - – n-hexane)
134	nBu	H		H	H		Single bond	111-113 (diethylether – n-hexane)

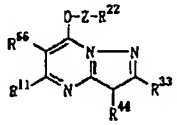
(0068)

Table 5 (continued)

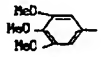
Example No.	R1	R5	R2	R3	R4	R6	A	Melting point (°C) (Re-crystallisation solvent)
135	HOOC-C_3H_6-	H		H	H	H	Single bond	191-193 (ethanol – n-hexane)

(0069)

Table 6



Me: methyl group, n-Bu: n-butyl group.

Example No.	R11	R22	R33	R44	R55	Z	Melting point (°C) (Re-crystallisation solvent)
136	n-Bu		H	H	H	$-CH_2-$	100-103 (ethyl acetate – n-hexane)

(0070)

Each compound represented by general formula (1) and general formula (2) can be made into the acid addition salt which is pharmacologically permitted, and such salts or the like is also included as effective ingredient compound of adenosine potentiator of this invention. As the acid which can form the aforesaid acid addition salt, inorganic acid such as hydrochloric acid, hydrobromic acid, sulfuric acid or the like, organic acid such as oxalic acid, fumaric acid, maleic acid, tartaric acid, citric acid or the like can be given as examples, and formation reaction of this acid addition salt can follow normal method.

(0071)

Moreover, in accordance with normal methods otherwise, the ones wherein compounds represented by general formula (1) wherein R^6 is hydrogen atom can be made into alkali metal salt, for example sodium salt, potassium salt and the like, alkaline earth metal salt, for example calcium salt, magnesium salt and the lik, and other salt such as cuprate or the like,

are also included as effective ingredient compound of adenosine potentiator of this invention.

(0072)

Moreover, among compound represented by general formula (1), some of the compounds wherein R^1 is lower alkenyl group, and compounds wherein A is alkenylene group can take cis, trans isomer structure, the adenosine potentiator of this invention can include any such isomers as an active ingredient.

(0073)

Moreover, for some of the compounds represented by general formula (1), the optical isomer with carbon atom as asymmetric center is present, and adenosine potentiator of this invention can contain as an active ingredient any such optically active substance and racemate.

(0074)

Adenosine potentiator of this invention has at least one member selected from the compound which represented by general formula (1) and the compound which represented by general formula (2) as effective ingredient. This is made into a general drug preparation composition using suitable non-toxic carrier, and used.

(0075)

As the aforesaid carrier used for drug preparation of this invention, diluent or excipient corresponding to conditions of use of preparation such as usually used filler, expander, binding agent, humectant, disintegrating agent, surface active agent, lubricant which usually is used or excipient can be given as example and these are suitably selected corresponding to administration unit form of preparation to be obtained and used.

(0076)

As administration unit form of the aforesaid drug preparation, various forms can be selected corresponding to therapy objective, and, as representative examples thereof, tablet, pill, powder, liquid agent, suspension, emulsion, granule, encapsulated formulation, suppository, injection (liquid agent, suspension or the like), ointment and the like may be proposed.

(0077)

When forming into tablet, the aforesaid preparation carrier is for example excipient such as lactose, refined sugar, sodium chloride, glucose, urea, starch, calcium carbonate, kaolin, crystalline cellulose, silica, potassium phosphate and the like, binding agent such as water, ethanol, propanol, single syrup, glucose liquid, starch liquid, gelatin solution, carboxymethylcellulose, hydroxypropylcellulose, methyl cellulose, polyvinylpyrrolidone and the like, disintegrating agent such as carboxymethylcellulose sodium, carboxymethylcellulose calcium, low degree of substitution hydroxypropylcellulose, dry starch, sodium alginate, agar powder, laminaran powder, sodium bicarbonate, calcium carbonate and the like, surfactant such as polyoxyethylene sorbitan fatty acid esters, sodium lauryl sulfate, stearic acid monoglyceride and the like, inhibitor of disintegration such as refined sugar, stearin, cacao butter, hydrogenated oil or the like, adsorption enhancer such as quaternary ammonium salt group, sodium lauryl sulfate and the like, moisture retaining agent such as glycerol, starch and the like, adsorbent such as starch, lactose, kaolin, bentonite, colloidal silica or the like, lubricant such as purified talc, stearate, boric acid powder, polyethyleneglycol and the like can be used. Further the tablet can be made into the tablet coated with ordinary agent coating in accordance with requirements, for example sugar coated tablet, gelatin encapsulation tablet, enteric coated tablet, film coating tablet or double tablet, multilayer tablet.

(0078)

When formed into the form of a pill, excipient such as for example carrier such as glucose, lactose, starch, cacao butter, hardened vegetable oil, kaolin, talc and the like, binding agent such as powdered gum arabic, tragacanth powder, gelatin, ethanol and the like, disintegrating agent such as laminaran, agar and the like can be used as preparation carrier.

(0079)

When formed into a form of suppository, as preparation carrier, for example polyethyleneglycol, cacao butter, higher alcohol, esters of higher alcohol, gelatin, semi-synthetic glyceride and the like can be used.

(0080)

Encapsulated formulation is usually prepared according to normal method, by mixing

effective ingredient compound of this invention with the various preparation carrier exemplified above and packing into hard gelatin capsule, soft capsule and the like.

(0081)

When prepared as injection agent such as liquid agent, emulsion, suspension and so on, such materials are sterilized and preferably made isotonic with blood, and when formed into such forms, as a diluent, for example, water, ethanol, macrogol, propylene glycol, ethoxylation isostearyl alcohol, polyoxyisosteary alcohol, polyoxyethylene sorbitan fatty acid ester species as can be used. Moreover, in this case, sufficient sodium chloride, dextrose or glycerol to form an isotonic solution may be contained in agent of this invention, and moreover ordinary solubilizer, buffer agent, analgesic or the like may be added.

(0082)

Furthermore, in agent of this invention, colorant, preservative, odorant, flavor agent, sweetener and so on and other pharmaceutical can be contained in accordance with requirements.

(0083)

When formed into a form of ointment such as paste, cream, gel and the like, for example white petrolatum, paraffin, glycerol, cellulose derivative, polyethyleneglycol, silicone, bentonite and the like can be used as diluent.

(0084)

The amount of effective ingredient compound represented by general formula (1) and general formula (2) to be contained in the agent of this invention is suitably selected from a wide range without restriction in particular, but usually one containing an amount of about 1-70 wt.% approximately in the drug preparation is satisfactory.

(0085)

Administration method of the aforesaid drug preparation is not limited in particular, and it is determined corresponding to various formulations, age of patient, the distinction of sex, other conditions, degree of disease or the like. For example, tablet, pill, liquid agent, suspension,

emulsion, granule and encapsulated formulation are administered orally, and injection is used alone or mixed with ordinary adjuvant fluid such as dextrose, amino acid or the like, and administered intravenously, and further it is administered alone intramuscularly, intracutaneously, subcutaneously or intraperitoneally in accordance with requirements, and, the suppository is administered rectally.

(0086)

The dose of the aforesaid drug preparation is suitably selected by using the method of use thereof, age of patient, the distinction of sex, other conditions, degree of disease or the like, but usually the amount of the compounds of this invention which are effective ingredient of about 0.5-20 mg per 1 kg bodyweight per day is satisfactory, and said preparation can be administered by being divided and given 1-4 times per day.

(0087)

Examples

Hereinafter, in order to describe this invention further in detail, Preparation Examples of adenosine potentiator of this invention is given and thereafter, Pharmacological Test Examples are shown.

(0088)

Preparation Example 1

Preparation of encapsulated formulation.

Using 5-n-butyl-7-(3,4,5-trimethoxy benzoylamino) pyrazolo[1,5-a]pyrimidine as effective ingredient compound, hard gelatin capsules (1000 capsules) containing 250 mg per 1 capsule was prepared by the following formulation.

(0089)

Effective ingredient compound	250 g
Crystalline cellulose (Pharmacopeia of Japan product)	30 g
Corn starch (Pharmacopeia of Japan product)	17 g
Talc (Pharmacopeia of Japan product)	2 g
Magnesium stearate (Pharmacopeia of Japan product)	1 g

mM, $NaHCO_3$ 25 mM, glucose 11 mM) under pressure of 1 g, and it was aerated continuously with O_2 / CO_2 (95 % / 5 %) mixed gas.

(0093)

While applying electric stimulation of 25 V to this ileum with cycle of 0.1 Hz, adenosine was cumulatively added from 10^{-8} M to the organ bath and the adenosine concentration to inhibit 100 % of the spasmodic contraction by the electric stimulation was determined (control group).

(0094)

Moreover, spasmodic contraction was measured using an isotonic transducer (TD-111T made by Nihon Kohden) and it was recorded with recorder (NIHON DENSI KAGAKU, U-228).

(0095)

On the other hand, at 30 minutes before the addition of adenosine, 10^{-6} M (group 1 of this invention) or 3 x 10^{-6} M (group 2 of this invention) of 5-n-butyl-7-(3,4,5-trimethoxy benzoylamino) pyrazolo[1,5-a]pyrimidine was added to the organ bath, and the adenosine concentration to inhibit 100 % of the spasmodic contraction by the electric stimulation was determined in the same way as described above.

(0096)

As a result, the adenosine concentration to inhibit 100 % of the contraction was 10^{-6} M in group 1 of this invention, and 3 x 10^{-7} M in the group 2 of this invention, and compared to the control groups, it fell by 1/3 and 1/10 respectively. Therefore, it became clear that the effective ingredient compound of this invention showed excellent adenosine potentiation action.

(0097)

Pharmacological Test Example 2

Hartley series male guinea pigs (10 weeks old, 400-450 g) were slaughtered by cervical spine dislocation, heart was isolated, and atrium was separated. After confirming the spontaneous contraction of atrium, this was suspended in organ bath containing 10 ml Krebs • Henseleit

liquid (NaCl 118 mM, KCl 4.7 mM, $CaCl_2$ 2.5mM, KH_2PO_4 1.2 mM, $MgSO_4$ 1.2 mM, $NaHCO_3$ 25 mM, glucose 11 mM) under pressure of 1 g, and it was aerated continuously with O_2 / CO_2 (95 % / 5 %) mixed gas.

(0098)

Adenosine was cumulatively added from 3 x 10^{-7} M to the organ bath, and the adenosine concentration at which spontaneous contraction of atrium began to be inhibited was determined (control group).

(0099)

Moreover, the spontaneous contraction of atrium was measured using isotonic transducer (TD-111T made by Nihon Kohden), it was amplified with biogenic amplifier (Nihon Kohden, TB-611T), and thereafter it was recorded with a recorder (NIHON DENSIKAGAKU, U-228).

(0100)

On the other hand, at 10 minutes before the addition of adenosine, 3 x 10^{-6} M (group 1 of this invention) or 10^{-5} M (group 2 of this invention) of 5-n-butyl-7-(3,4,5-trimethoxy benzoylamino) pyrazolo[1,5-a]pyrimidine was added to organ bath, and the adenosine concentration at which spontaneous contraction of atrium began to be inhibited was determined in the same way as described above.

(0101)

As a result, the adenosine concentration at which 100 % inhibition of the contraction began was 3 x 10^{-7} M in the group 1 of this invention, 10^{-7} M in the group 2 of this invention, a fall of 1/10 and 1/30 respectively compared with the control group. Therefore, it became clear that the effective ingredient compound of this invention showed excellent adenosine potentiation action.

(0102)

Pharmacological Test Example 3

Hartley series male guinea pigs (10 weeks old, 350-400 g) were slaughtered by cervical spine

dislocation, ileum was isolated and the contents and unnecessary tissues were eliminated, then longitudinal muscle was peeled. The peeled longitudinal muscle was attached to a cannula fixed with an electrode, and it was aerated with O_2 / CO_2 (95 % / 5 %) mixed gas, and it was suspended in the Magnus tube filled with Krebs / Henseleit liquid (NaCl 118.3 mM, KCl 4.7 mM, $CaCl_2$ 2.5mM, KH_2PO_4 1.2 mM, $MgSO_4$ 1.2 mM, $NaHCO_3$ 25.0 mM, glucose 11.1 mM) at 37 °C, in such a way that the longitudinal muscle did not directly touch the electrode.

(0103)

To the aforesaid longitudinal muscle, square pulse electric stimulation of duration 0.5 msec. was applied with cycle 0.1 Hz using stimulator (made by Dia Medical System Co., type DPS-06) and when the nerve stimulated contraction had stabilised, adenosine was cumulatively added from 0.1 μM to the Krebs • Henseleit liquid, and IC50 of nerve stimulation contraction inhibitory action was determined.

(0104)

The aforesaid IC50 value was calculated from the adenosine concentration and inhibition ratio of two points before and after the inhibition ratio of 50 %. Moreover, the nerve stimulated contraction was measured using FD pickup (made by Nihon Kohden Co., type TB-611T) and amplifier (type AP-601G made of by Nihon Kohden Co.).

(0105)

On the other hand, at five minutes before the addition of adenosine, as test compound, compounds shown in the said each table was added as dimethylsulfoxide solution with concentration of 1 μM and IC50 of nerve stimulated contraction inhibitory action of adenosine was determined in the same way as above. Moreover, the ratio of IC50 of test compound non addition with respect to this value was calculated, and potentiation degree was calculated.

(0106)

The results are shown in following Table 7.

(0107)

Table 19

Test compound (Example no.)	Potentiation degree
1	4.8
16	7.6
19	6.9
53	8.4
55	5.1
75	6.0
100	2.7
111	2.7
135	2.6
136	7.1

(0108)

From the aforesaid table, effective ingredient compound of this invention clearly showed excellent adenosine potentiation action.

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